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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/918,740	07/31/2001	Frederick M. Hahn	KAS-103XC1	2719

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EXAMINER	
KRUSE, DAVID H	

ART UNIT	PAPER NUMBER
1638	

DATE MAILED: 01/28/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/918,740	HAHN ET AL.	
	Examiner	Art Unit	
	David H Kruse	1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 November 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *16-20 and 56* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16-20 and 56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

STATUS OF THE APPLICATION

1. This Office action is in response to the Amendment and Remarks filed 10 November 2003.

2. Claims 1-15, 21-55 and 57-144 have been cancelled.

3. The Examiner has attached a PTO-892 form citing the references submitted in the Appendix filed 10 November 2003.

4. Those rejections not specifically addressed in this Office action are withdrawn in view of Applicant's amendments and/or arguments.

5. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 112

6. Claims 16-20 and 56 remain rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This rejection is repeated for the reason of record as set forth in the last Office action mailed 6 May 2003. Applicant's arguments filed 10 November 2003 have been fully considered but they are not persuasive.

Applicant argues that even though the claims do not require an absence of effects on plant growth and survival, ample evidence that increased isoprenoid production can be effected in both microbes and plants without serious affecting growth and survival (page 5, 2nd paragraph of the Remarks). This argument is not found to be

persuasive because Applicant relies upon teachings in the art directed to overexpression of a single enzyme involved in a specific isoprene synthesis pathway and does not address the issue of introducing the entire mevalonate pathway into a transgenic plant, for example. The issue concerning overexpression of specific enzymes in the mevalonate pathway in a plant remains.

Applicant argues that Chappell (1995) showed that increasing expression of merely one enzyme of the mevalonate pathway was indeed capable of directing more carbon into the isoprenoid pathway (page 6, 1st paragraph of the Remarks). This argument is not found to be persuasive because the premise of Chappell was that increasing the HMGR enzyme in the transgenic plant would have been expected to increase the level of normal end-product sterols, which it did not, hence the issue of unpredictability remains in overexpressing enzymes in the mevalonate pathway in a plant remains. It is Applicant's burden to teach one of skill in the art how to make and use the claimed invention. Simply increasing a pool of sterols without increasing the useful sterols one would expect a plant to produce does not teach how to use the invention as broadly claimed.

Applicant argues that Applicant's invention involves introducing into target cells a polynucleotide for the mevalonate pathway *in toto* (page 7, 1st paragraph of the Remarks). Applicant argues that Martin *et al* (2003) enables the claimed invention because Martin *et al* teach use of the entire mevalonate pathway was superior to isolated elements in terms of delivering high-level precursors and engineering of the entire pathway into a cell naturally lacking the pathway circumvents any control

mechanism of the pathway expression since no native regulatory elements are present (page 7, 2nd paragraph of the remarks). This argument is not found to be persuasive because Martin *et al* teach that transformation of *E. coli* with a polynucleotide encoding the complete mevalonate pathway was successful because *E. coli* lacks the pathway, but that plants and yeast, for example *Saccharomyces cerevisiae* from which the mevalonate pathway encoding genes were produced to transform *E. coli*, would be subject to regulatory issues (see page 797, left column, 1st paragraph, and page 800, left column, last paragraph of Martin *et al*, 2003). Martin *et al* also teaches that coexpression of a synthetic sequiterpene synthase was required to overcome the cell growth inhibition resulting from expression of the heterologous mevalonate pathway in *E. coli* (page 800, left column, bottom of last paragraph).

Applicant argues that it is well known in the art that use of an isolated heterologous enzymatic component may have lower functioning in a particular host, but nevertheless it may demonstrate some activity and that it is obvious to anyone skilled in the art that one can substitute one cDNA for another from a different source to affect altered activity in a particular host. Applicant also argues that the art has taught, in reference to the teachings of Martin *et al* 2003, that insertion of the complete mevalonate pathway has been shown to be fully functional and to affect increased flux in the isoprenoid pathway (page 7, 3rd paragraph of the remarks). This argument is not found to be persuasive because it is Applicant's burden to teach one of skill in the art how to make and use the invention within the full breadth of the claims without undue trial and error experimentation. It is the Examiner's opinion that it would have required

undue trial and error experimentation by one of skill in the art at the time of Applicant's invention to combine a myriad of cDNAs encoding each of the six enzymes of the mevalonate pathway from different sources in order to practice the claimed invention in any host cell, and especially in plants. In addition, Martin *et al* teaches that coexpression of an additional enzyme was required in *E. coli* due to the effects of expression of the mevalonate pathway from *S. cerevisiae* as discussed above.

Applicant argues that as to the assertions regarding polycistronic polynucleotides, Applicants note that their specification teaches insertion of a polycistronic polynucleotide into 1) a prokaryotic host in which polycistronic operons are the norm; and into 2) the plastids (for example, chloroplast) of microalgae and higher plant cells in which polycistronic operons are also the norm based on their prokaryotic origin. Applicant argues that expression of such polycistronic polynucleotides is entirely predictable because this is natural for bacteria and plastids of plant cells as is well known in the art by R. Bock (2001) J. Mol. Biol., Vol. 312, pages 425-438 (page 8, 1st paragraph of the Remarks). This argument is not found to be persuasive because the claims as directed to plants are not limited to transformation of plastids. In addition, the issues raised by Martin *et al* (2003) as discussed above would be applicable to transformation of plant plastids with a polynucleotide encoding the mevalonate pathway. Bock (2001) teaches that transplastomic technologies are still far from being routine tools for plant biotechnologist and some technical limitations have still to be overcome (page 435, left column, 3rd paragraph). Because Applicant has not reduced to practice the claimed invention, Applicant has provided no guidance to one of skill in the art how

to overcome the shortcomings of the claimed invention using such a non-routine method in plants.

Applicant's arguments as directed to premature translation termination of polycistronic polynucleotides expressed in plants cannot be addressed by the Examiner as directed to the teachings of Hunt and Maiti (2001) because Applicant has not supplied the information and it is not readily available to the Examiner (paragraph spanning pages 8-9 of the Remarks). As to Applicants argument that one of ordinary skill in the art would have expected that a large number of cistrons could be translated in plants, it remains unclear from the teachings of the art if expression of polycistronic polynucleotides is predictable in plants as Applicant asserts without undue trial and error experimentation.

Applicant argues that it would be know to anyone skilled in the art in view of Applicants' teaches, a polynucleotide can comprise a series of open reading frames with their own regulatory elements that enable transcription and subsequent protein targeting to the organelle in which it is function and that nuclear multigene engineering specific to isoprenoid production in plants is taught in the art (page 9, 2nd paragraph of the Remarks). The Examiner concedes that multiple transgenes encoding enzymes in a metabolic pathway can be co-transformed into a plant, but the example of Ye *et al* (Science 287:303-305 (2000)) directed to introducing the beta-carotene biosynthetic pathway into rice does not specifically enable introduction of the mevalonate pathway into any host cell as claimed by Applicant.

. Applicant argues that each of Martin *et al* (2003) referred to above; WO 02/099095, Lopez-Ulibarri *et al.*, published December 12, 2002; and U.S. 2003/148479, Kim Seon-Won *et al*, published August 7, 2003 discusses construction of operons containing genes which encode enzymes of the mevalonate pathway, which genes are heterologous to the intended target cells, and which show successful expression in the target organisms of the heterologous polynucleotides. Applicant argues that these successes confirm the truth of Applicants' teachings regarding the ability of the skilled artisan to obtain heterologous polynucleotide sequences encoding enzymes of the mevalonate pathway, combine these polynucleotides into a functional operon, and successfully introduce the operon into a target cell, wherein it is expressed (page 10, 2nd paragraph of the Remarks). The Examiner notes that U.S. 2003/148479, Kim Seon-Won *et al*, published August 7, 2003 could not be found and that a search for the inventor was unsuccessful, Applicant did not supply a copy of this reference. Applicant's arguments are not found to be persuasive, especially in view of the teachings of Martin *et al* (2003) as discussed supra. In addition, Lopez-Ulibarri *et al* only teach transformation of bacteria, especially *E. coli,* with a polynucleotide encoding the mevalonate pathway and not plants.

Applicants argues that Exhibit A hereto which is proof of an actual reduction to practice of the teachings of Examples 1 through 7 of the subject application. Applicant argues that Exhibit A shows map and restriction analysis of Applicants' vector pHKO2, confirming that it contains orfs encoding the complete mevalonate pathway, and confirming that introduction of this vector into target cells resulted in expression of the

enzymes of the complete mevalonate pathway, proving that pHKO2 was effective in providing a mevalonate pathway to organisms previously lacking such, resulting in synthesis of IPP from acetyl-CoA, further confirming the truth of Applicants' teachings (page 10, 3rd paragraph of the Remarks). This argument is not fully persuasive because the information supplied is insufficient for the Examiner to determine the scope of enablement of the claimed invention because there are insufficient details as to what is being presented. In addition, Applicant is advised to present such evidence of diligence and enablement in the form of a 37 CFR 1.132 declaration.

Applicant argues that Applicants have taught that those skilled in the art should obtain polynucleotides encoding enzymes of the complete mevalonate pathway, construct plasmids containing functional operons thereof, and introduce these plasmids into target cells wherein they will function to produce increased isoprenoid production as compared to non-transformed cells and that none of these steps requires undue experimentation (page 10, 4th paragraph of the Remarks). This argument is not found to be persuasive because Applicant is required to enable the invention within the full scope of the claims such that one of skill in the art would not be required to practice undue trial and error experimentation, or to perfect Applicant's invention. As discussed supra, it remains evident that expression of the mevalonate pathway by transformation of a polynucleotide encoding all of the enzymes in said pathway is unpredictable, and appears to require additional method steps or critical features in order to practice the invention as broadly claimed.

Conclusion

7. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

8. No claims are allowed.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David H. Kruse, Ph.D. whose telephone number is (571) 272-0799. The examiner can normally be reached on Monday to Friday from 8:00 a.m. to 4:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Amy Nelson can be reached at (571) 272-0804. The fax telephone number for this Group is (703) 872-9306 Before Final or (703) 872-9307 After Final.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group Receptionist whose telephone number is (703) 308-0196.

Amy Nelson

David H. Kruse, Ph.D.
23 January 2004

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